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UNITED STATES DISTRICT COURT
DISTRICT OF UTAH

NUTRACEUTICAL CORPORATION and SOLARAY, INC.,	)	
Plaintiffs,	)	
v.	)	Case No. 2:04CV00409 TC
LESTER CRAWFORD, D.V.M., Acting Commissioner, U.S. Food and Drug Administration, et al.,	)	
Defendants.	)	

DEFENDANTS' REPLY TO PLAINTIFFS' OPPOSITION TO DEFENDANTS' CROSS-MOTION FOR SUMMARY JUDGMENT

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I. INTRODUCTION

Plaintiffs' challenges to the validity of the FDA's regulation ("Final Rule")[1] lack merit because the Rule complies with both the Dietary Supplement Health and Education Act of 1994 ("DSHEA") and the Administrative Procedure Act ("APA"). First, FDA's interpretation of "unreasonable risk" is a reasonable and plausible construction of DSHEA, 21 U.S.C. § 342(f)(1)(A). Second, FDA considered dosage in conducting a risk-benefit analysis of EDS. Third, the science contained in the administrative record establishes that ephedrine alkaloid-containing dietary supplements ("EDS") containing 10 mg or less of ephedrine alkaloids per daily dose are adulterated, and Plaintiffs' new matters not raised in comments before the agency are waived. Fourth, FDA's regulation of EDS in a manner that may differ from its regulation of conventional foods is appropriate because such difference is directed by the Federal Food, Drug, and Cosmetic Act ("FDCA"). And finally, FDA followed the APA rulemaking procedures in promulgating the Final Rule.

II. THE FINAL RULE COMPORTS WITH 21 U.S.C. § 342(f)(1)(A) AND THE APA

A. FDA'S STATUTORY CONSTRUCTION OF 21 U.S.C. § 342(f)(1)(A)

In the Final Rule, FDA concluded that, based on the plain meaning of the statutory

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[1] Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk, 69 Fed. Reg. 6788 (Feb. 11, 2004); see Administrative Record ("A.R.") at 105594-855. Citations to reference numbers ("Ref.") correspond to the documents referenced in the Final Rule and listed in section XII of the Rule. 69 Fed. Reg. at 6849-53.

language, as well as the usage of the same language in another part of the FDCA,[2] "Congress unambiguously intended that an assessment of 'unreasonable risk' in the dietary supplement context should entail a risk-benefit analysis." 69 Fed. Reg. at 6823. FDA's interpretation of "unreasonable risk"[3] to encompass a weighing of the risks and benefits is neither arbitrary nor capricious, and indeed is the most reasonable reading of the relevant language.

Plaintiffs contend that the Final Rule imposes a requirement that dietary supplements must have a proven benefit as a "condition precedent to saleability," and that such requirement is

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[2] Plaintiffs misunderstand FDA's cite to the medical device classification provisions. See Pl. Opp. at 21, n.35. FDA does not contend that Congress patterned 21 U.S.C. § 342(f)(1)(A) after those provisions, nor that medical devices and dietary supplements are regulated in the same manner. Rather, the legislative history for the medical device classification provisions lends support to FDA's interpretation of "unreasonable risk," because Congress there indicated that "unreasonable risk" requires a weighing of risks and benefits. A basic canon of statutory construction is that "identical words used in different parts of the same act are intended to have the same meaning." Sullivan v. Stroop, 496 U.S. 478, 484 (1990) (internal citations omitted). And, as explained in the Final Rule, "[t]here is nothing in the provisions of the act dealing with dietary supplements, or the legislative history thereof, that would suggest that FDA should interpret the term 'unreasonable risk' in the context of dietary supplements differently than it does in the context of medical devices." 69 Fed. Reg. at 6823. Indeed, Plaintiffs themselves admit that this Court should interpret the "Act [the FDCA] as a whole." Pl. Opp. at 11.

[3] Plaintiffs argue that in order to find EDS adulterated under 21 U.S.C. § 342(f)(1)(A), FDA would have to conclude that EDS pose both a significant and unreasonable risk of illness or injury. See Pl. Opp. at 3-5. This is contrary to the statutory language. Section 342(f)(1)(A) provides that a dietary supplement is adulterated if it "presents a significant or unreasonable risk of illness or injury" (emphasis added), and "[w]hen the term 'or' is used, it is presumed to be used in the *disjunctive* sense unless the legislative intent is clearly contrary." United States v. O'Driscoll, 761 F.2d 589, 597 (10th Cir. 1985) (emphasis in original). There is nothing in the legislative history cited by Plaintiffs to suggest that Congress intended the word "or" to be read as "and." In fact, as Plaintiffs note, an earlier version of DSHEA read "presents a substantial and unreasonable risk of illness or injury. . .," Pl. Opp. at 21, n.35, but the enacted version instead reads "significant or unreasonable risk." Congress is presumed to intend the language it enacts, see, e.g., Barnhart v. Sigmon Coal Co., 534 U.S. 438, 462 (2002), and hence FDA acted properly in enacting the Final Rule under just the "unreasonable risk" prong of 21 U.S.C. § 342(f)(1)(A).

contrary to the FDCA. Pl. Opp. at 21-22. The Final Rule applies only to EDS, not all dietary supplements. Moreover, the Final Rule does not establish pre-market requirements for dietary supplements. The Rule merely finds that, pursuant to 21 U.S.C. § 342(f)(1)(A), EDS pose an unreasonable risk of injury, and are therefore adulterated and can no longer lawfully be marketed. In the Final Rule, FDA explained that the "unreasonable risk" language of 21 U.S.C. § 342(f)(1)(A) requires a risk-benefit analysis to determine whether dietary supplements are adulterated. FDA considered the benefits of EDS as part of this analysis, not to determine whether EDS could be marketed in the first instance, as Plaintiffs suggest. This is precisely what the FDCA requires.

Plaintiffs also assert that FDA failed "to provide the regulated class sufficient guidance to discern when a dietary ingredient will be adulterated" by not adequately defining "unreasonable risk" or "benefit" in the Final Rule, in violation of the APA, 5 U.S.C. § 706(2)(A). Pl. Opp. at 23-24. The Final Rule fully explains FDA's interpretation of "unreasonable risk" and the details of the risk-benefit analysis that FDA conducted, including all the evidence FDA evaluated and its scientific views about that evidence, see 69 Fed. Reg. at 6798-6827, as outlined in the government's earlier filing. See Def. Mem. at 32-33.

Plaintiffs' contention that FDA did not "explain what kind, degree, nature, quality, or quantity of 'benefit'" would be necessary to outweigh an identified risk is unpersuasive. The Final Rule states that FDA "considered only known and reasonably likely benefits, not speculative benefits." 69 Fed. Reg. at 6798. FDA defined "reasonably likely benefit" as a benefit "that is supported by a meaningful totality of the evidence, given the current state of the

scientific knowledge." Id. FDA further explained:

> We give more weight to benefits that improve health outcomes, especially in the long term, than to benefits that are temporary or rely on subjective measures such as feeling or looking better. For example, sustained, long-term weight loss in an obese or overweight person is a much more important benefit than short-term weight loss because long-term weight loss in these individuals reduces the risk of serious morbidity and mortality (e.g., heart attacks and strokes), while short-term weight loss does not.

Id. at 6799. In light of the numerous pages of the Final Rule dedicated to FDA's analysis of the potential benefits of EDS, in addition to those pages detailing FDA's risk-benefit analysis, Plaintiffs' argument that "[i]t is entirely unclear what kind of benefit will be sufficient to overcome any perceived risk," Pl. Opp. at 24, simply lacks merit.

FDA's interpretation of 21 U.S.C. § 342(f)(1)(A) is consistent with the unambiguous statutory language. Even if this Court were to find the statutory language ambiguous, FDA's interpretation is reasonable and should be granted Chevron deference. See Def. Mem. at 26-30. Hence, this Court should reject Plaintiffs' claim that FDA's interpretation of "unreasonable risk" renders the Final Rule arbitrary and capricious under the APA.

B. THE FINAL RULE ESTABLISHES THAT, REGARDLESS OF DOSE, EDS PRESENT AN UNREASONABLE RISK OF ILLNESS OR INJURY

Plaintiffs argue that "[u]nder the Defendants' schema, a dietary ingredient can be declared adulterated *at every dose level* if the dietary ingredient presents an unreasonable risk *at some dose level*." Pl. Opp. at 15. This argument distorts Defendants' position and the approach taken by the Final Rule. As described in the Final Rule's preamble, and presented in Defendants' cross-motion for summary judgment, the agency relied on scientific studies and expert reviews

that evaluated the effects of EDS use at different dose levels, including low doses. See Def. Mem. at 32-37, 43-46. Based on all available scientific information, the agency found that EDS expose users to several risks, including stroke and heart attack that can result in death, id. at 33, and that even a dose of 1.5 mg every 4 hours (a daily dose of 9 mg)[4] would produce adverse health effects,[5] id. at 36. Furthermore, FDA concluded that, at all doses, EDS have an unfavorable risk-benefit ratio. Id. at 36-37; see also id. at 45-46 ("Regardless of dose, the minimal benefits of EDS are outweighed by the substantial risks associated with the use of these products.") Thus, Plaintiffs' allegation that FDA failed to consider dosage in conducting a risk-benefit analysis of EDS use is demonstrably incorrect.[6]

Defendants also dispute Plaintiffs' implication that, if FDA seeks to ban a particular product by declaring it to be adulterated under 21 U.S.C. § 342(f)(1)(A), there must exist clinical trials studying the effects of every conceivable dosage of that product before FDA can effect a ban. See Pl. Opp. at 7-8, 13. Any requirement for clinical trial data at every conceivable dosage for FDA to declare a dietary supplement, at all doses, to be adulterated is illogical and unrealistic. See Def. Mem. at 44-45. It is wholly appropriate for experts to draw conclusions regarding

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[4] FDA found that, although dosages vary in EDS, most products are labeled with 20-25 mg ephedrine alkaloids per recommended serving and 100-150 mg ephedrine alkaloids per day. 69 Fed. Reg. at 6805.

[5] Plaintiffs now concede that their EDS product has up to 13 mg ephedrine alkaloids per daily dose. See Pl. Opp. at 16, n.30.

[6] Plaintiffs' assertions regarding the implications of FDA's analysis are similarly wrong. See Pl. Opp. at 15, 20 note 34 and accompanying text. Allegations that, under the Final Rule's "schema," all dietary ingredients are capable of being banned because all such ingredients present an unreasonable risk at some dose level ignore FDA's careful risk-benefit analysis.

dosages not specifically studied in clinical trials from scientific evidence that is available.

C. THE SCIENCE IN THE ADMINISTRATIVE RECORD ESTABLISHES THAT EDS CONTAINING 10 MG OR LESS EPHEDRINE ALKALOIDS PER DAILY DOSE ARE ADULTERATED

Plaintiffs present this Court with a critique of certain scientific material on which FDA relied to conclude that all EDS, including dietary supplements containing daily dosages of ephedrine alkaloids alleged to be in Plaintiffs' product, present an unreasonable risk of illness or injury. Plaintiffs, however, do not rely on the administrative record to corroborate their assertions. Their "technical" viewpoint of the safety of their EDS product stands unsupported.

Plaintiffs acknowledge – as they must – that review of the agency's action here is limited to the administrative record. See Pl. Opp. at xiv; see also Def. Mem. at 24-25. Although Plaintiffs claim they do not seek to "present any new, extrarecord science," Pl. Opp. at xiv, that is precisely what they seek to do with their "scientific" critique of the data underlying the Final Rule. See, e.g., Pl. Opp. at 8-10 (disputing that EDS containing 10 mg or less ephedrine alkaloids per daily dose would produce adverse health effects). It is well established that issues not raised in comments before the agency are waived, and Plaintiffs' efforts to introduce new material here should be completely disregarded. See, e.g., New Mexico Envtl. Improvement Div. v. Thomas, 789 F.2d 825, 835-36 (10th Cir. 1986).

For another reason, Plaintiffs' extrarecord material should be accorded no weight. In numerous instances, Plaintiffs' counsel are making arguments challenging the validity of scientific studies and expert reviews that counsel are not qualified to make. See, e.g., Pl. Opp. at 8-10 (disputing that EDS containing 10 mg or less ephedrine alkaloids per daily dose would

produce adverse health effects); see also id. at xxi-xxv, ¶ 17 and at 18, n.33 (challenging the well-established scientific finding that higher blood pressure has adverse health effects because it increases the risk of cardiovascular disease); see also id. at xviii-xxi, ¶¶ 12, 14-16 (contesting the Boozer study findings that the ephedra group had statistically significantly higher average blood pressure measurements over a 24-hour period after one month of continued exposure compared with the placebo group, 69 Fed. Reg. at 6801-02; Def. Mem. at 15-16, ¶¶ 14-16). Without expert evidence supporting those arguments – and Plaintiffs do not and cannot offer any – the arguments present no challenge to the wealth of scientific information that formed the basis of the agency's action in this instance. Cf. Cactus Corner, LLC v. Dep't of Agric., No. CIV-F-02-6270, 2004 WL 2785611 (E.D. Cal. March 11, 2004) (finding that plaintiffs' "challenge to the science underlying the Rule and the conclusions the Agency reached, is no more than unfounded lay opinion," which amounts to "a failure of proof").

Counsel's criticisms are laden with inaccuracies. For example, based on a scientific review commissioned by FDA (the "Inchiosa review"), the agency documented that EDS, at a daily dose lower than 10 mg of ephedrine alkaloids (see supra at 5, n.5), "would produce cardiovascular effects that may be dangerous alone, or in association with risk factors." See Def. Mem. at 45 (internal quotations omitted). Plaintiffs repeatedly attack the Inchiosa review and FDA's related conclusions. See Pl. Opp. at 8-10. First, Plaintiffs dispute FDA's conclusion that all EDS, regardless of dose, are adulterated on the ground that the Inchiosa review is based on a pharmacological model, rather than a clinical trial. As noted, this argument lacks merit. See supra at pp. 5-6.

Second, Plaintiffs contend that the conclusions drawn from the Inchiosa review must be invalid because the model used intravenously administered epinephrine to evaluate the pharmacodynamic effects of orally administered ephedrine at particular dose levels. See Pl. Opp. at 8. However, the Inchiosa review fully explains the pharmacokinetic principles that form the basis of the model used. See, e.g., Ref. 84 at 1 [A.R. 107996] (noting that there are "good data available regarding the cardiovascular potency ratio between epinephrine and ephedrine"); id. at 3 [A.R. 107998] (explaining that the cardiovascular potency ratios can be used to make pharmacodynamic comparisons between epinephrine and ephedrine and that one can "relate the cardiovascular effects of various chronic oral doses of ephedrine to those of epinephrine i.v. infusion rates"); Ref. 85 at 15-16 [A.R. 108024-025] (discussing ephedrine's bioavailability, which assists in making predictions of its pharmacological effects).

Third, Plaintiffs mistakenly claim that the model is based on a 20 mg intake and that the model is inapplicable to intakes less than 20 mg of ephedrine alkaloids (or alternatively to intakes less than 40% of 20 mg of ephedrine alkaloids). See Pl. Opp. at 9-10. However, the model is not based on a 20 mg intake or any one particular intake value, but rather a proportional relationship between various chronic (repeated) ephedrine dosages and epinephrine infusion rates. See Ref. 84 at 4 [A.R. 107999].

Finally, Plaintiffs attempt to discredit one of the sources on which the Inchiosa review relies (i.e., the "Clutter study"). See Pl. Opp. at 10-11. Plaintiffs assert that the Clutter study "clearly demonstrates that an intake of ephedrine of 0.3 mgs every 4 hours, 24 hours a day, chronically, would not produce effects on hemodynamic variables (heart rate, systolic blood

pressure, diastolic blood pressure)." Id. at 10; see also id. at 13 (alleging that the Clutter study "demonstrates that at least 1.8 mg daily is completely safe"). Nowhere in the Clutter study can this, or any similar, statement be found; nor can it be "clearly" demonstrated.

D. THE FINAL RULE IS CONSISTENT WITH THE STATUTORY DIFFERENCES IN REGULATION OF DIETARY SUPPLEMENTS AND *CONVENTIONAL FOODS*

Plaintiffs argue that the Final Rule impermissibly causes conventional foods to be regulated differently from dietary supplements. See Pl. Opp. at 25-26. In attempting to convince the Court that FDA's action is arbitrary and capricious, Plaintiffs argue that, while FDA deemed EDS to be adulterated under 21 U.S.C. § 342(f)(1)(A), "food" (e.g., "ephedra tea") is permitted to be sold without restriction under the food adulteration provisions set forth at 21 U.S.C. § 342. Pl. Opp. at 26. As explained, see Def. Mem. at 45-46, where Congress expressly provided that dietary supplements be subject to the "unreasonable risk" standard that does not apply to conventional foods, FDA may implement that provision without being arbitrary and capricious.

E. THE FINAL RULE COMPLIES WITH NOTICE AND COMMENT RULEMAKING

Plaintiffs contend that, in promulgating the Final Rule, FDA created "a new standard for adulteration without advance notice that one was in the offing," in violation of the notice and comment requirements of the APA, 5 U.S.C. § 553. Pl. Opp. at 29-32. Plaintiffs argue that the risk-benefit analysis is the "central defining principle" in the Final Rule and that, because FDA did not give advance notice specifying that it would be using such analysis, Plaintiffs and the interested public lacked sufficient notice of the Final Rule. Id. at 28.

The Final Rule does not create a new standard for adulteration.[7] The "unreasonable risk" adulteration standard implemented by the Final Rule, 21 U.S.C. § 342(f)(1)(A), was enacted by Congress in 1994. The risk-benefit analysis contained in the Final Rule is merely FDA's interpretation of the "unreasonable risk" standard and is not a substantive rule that requires a separate rulemaking.[8] As previously explained, see Def. Mem. at 50, in the proposed rule and subsequent notices, FDA advised the public that it was considering regulating EDS under 21 U.S.C. § 342(f)(1)(A). See, e.g., 68 Fed. Reg. at 10419-20, 62 Fed. Reg. at 30693, 30695.

Nor was the public denied an opportunity for meaningful comment on the issues in the Final Rule. As explained in the Final Rule, FDA received numerous comments from the public concerning many aspects of the Final Rule, including the appropriateness of a risk-benefit analysis to determine whether EDS pose an unreasonable risk of injury or illness under 21 U.S.C. § 342(f)(1)(A). See, e.g., 69 Fed. Reg. at 6822. Notice is adequate if it fairly apprises the public of the issues involved in the rulemaking. See United Steelworkers of America, AFL-CIO-CLC v. Marshall, 647 F.2d 1189, 1221 (D.C. Cir. 1980).

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[7] Plaintiffs claim that "FDA admits it is creating a new standard 'of unreasonable risk under 402(f)(1)(A) of the Act [21 U.S.C. § 342(f)(1)(A)] for the first time.' 69 Fed. Reg. at 6794." Pl. Opp. at 33, n.56 (emphasis added). In fact, the Final Rule provides that FDA is "articulating a standard for unreasonable risk . . . for the first time," 69 Fed. Reg. at 6794 (emphasis added), rather than creating such a standard. See also Def. Mem. at 52.

[8] Plaintiffs state that neither the Final Rule nor the "Risk/Benefit Test" contained in the Final Rule constitute interpretive rules exempt from the notice and comment requirements. Pl. Opp. at 33-34. Defendants agree that the Final Rule is not an interpretive rule, but maintain that only the Final Rule, and not the risk-benefit analysis conducted by FDA in the Final Rule, is a substantive rule requiring notice and comment rulemaking.

III. CONCLUSION

For the foregoing reasons, as well as the reasons in Defendants' previous filing, this Court should deny Nutraceutical's Motion for Summary Judgment and grant Defendants' Cross-Motion for Summary Judgment.

Respectfully submitted,

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Dated: January 14, 2005

CERTIFICATE OF SERVICE

I hereby certify that on this 14th day of January, 2005, I caused to be served by regular mail, postage prepaid, copies of "DEFENDANTS' REPLY TO PLAINTIFFS' OPPOSITION TO DEFENDANTS' CROSS-MOTION FOR SUMMARY JUDGMENT" addressed as follows:

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